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RECTAL SUPPOSITORY  
[Chokucho toyo seizai]

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## SPECIFICATIONS

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### 1. Title of the Invention

Rectal Suppository

### 2. Claim

Rectal suppository so characterized that it contains at least one type of carboxylic acid selected from fatty acids with 8 to 14 carbon atoms, leucine, and nontoxic salts of these, and at least one base selected from amino sugar antibiotics, polysaccharides, peptides of 4000 or lower molecular weight, mercaptoproline derivatives, and nucleic acid compounds, and the content of carboxylic acids is 0.5 to 20 w/w% of the total suppository.

### 3. Detailed Description of the Invention

This invention pertains to a rectal suppository. More particularly, this invention pertains to a rectal suppository that has superior rectal absorption.

Bases such as amino sugar antibiotics, polysaccharides, peptides of 4000 or lower molecular weight, nucleic acid compounds, or mercaptoproline derivatives are generally absorbed poorly by oral administration, and are normally administered by injection.

Injections, however, are not always satisfactory because they involve pain, are inconvenient to use, and involve risks such as muscle contractions.

Reflecting on this situation, the present inventors conducted extensive research on administrative routes for these bases other than injection. As a result, they discovered that when a fatty acid with 8 to

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\*Numbers in the margin indicate pagination in the foreign text.

14 carbon atoms, leucine, or nontoxic salt of these is distributed at a particular composition ratio in a rectal suppository that has an amino sugar antibiotic, polysaccharide, peptide of 4000 or lower molecular weight, mercaptoproline derivative, or nucleic acid compound as its base, said base is absorbed extremely easily from the rectum into the bloodstream. With this, they perfected the present invention.

That is, this invention is a rectal suppository that contains at least one type of carboxylic acid selected from fatty acids with 8 to 14 carbon atoms, leucine, and nontoxic salts of these, and at least one base selected from amino sugar antibiotics, polysaccharides, peptides of 4000 or lower molecular weight, mercaptoproline derivatives, and nucleic acid compounds, and the content of carboxylic acids is 0.5 to 20 w/w% /2 of the total suppository.

Fatty acids with 8 to 14 carbon atoms used in this invention may be obtained naturally or synthetically, but ideally are obtained naturally. Either straight-chain or branching acids may be used for said fatty acids, but preferably, straight-chain fatty acids are used. In addition, fatty acids used may be either saturated or unsaturated.

Carbon atoms in such fatty acids ideally number 10 to 12 (such as ~~capric acid or lauric acid~~), and more ideally 10 (such as capric acid).

"Nontoxic salts of fatty acids with 8 to 14 carbon atoms" in this invention refers to any salt that is pharmacologically permissible. Examples of such salts include alkali metallic salts (such as sodium salts or potassium salts) and organic basic salts (for example, basic amino acid salts such as arginine salts or lysine salts).

Concrete examples of said fatty acids and nontoxic salts of these include caprylic acid and its sodium salt, potassium salt, lysine salt,

and arginine salt; pelargonic acid and its sodium salt, lysine salt, and arginine salt; capric acid and its sodium salt, potassium salt, lysine salt, and arginine salt; undecenoic acid and its arginine salt; lauric acid and its sodium salt, potassium salt, lysine salt, and arginine salt; dodecanoic acid and its lysine salt; myristic acid and its sodium salt, potassium salt, lysine salt, and arginine salt; and undecylenic acid. Of these, the above-mentioned capric acid and its salts, and lauric acid and its salts are ideal.

Even more ideal are capric acid and its salts.

Fatty acids with 8 to 14 carbon atoms, leucine, and nontoxic salts of these may be used alone or by combining two or more types.

These fatty acids with 8 to 14 carbon atoms, leucine, and nontoxic salts are added to the rectal suppository at 0.5 to 20 w/w%, preferably 1 to 15 w/w%, and more preferably 3 to 10 w/w% of the total suppository.

Examples of amino sugar antibiotics used in this invention include gentamicin, dibecacin [transliteration], paulomycin, streptomycin, kanamycin, kanedomycin, rubidomycin, tobramycin, amikacin, flagiomyacin, and cysomycin [as transliterated]. Examples of polysaccharides include heparin and polysaccharide antitumor substances. Examples of "polysaccharide antitumor substances" here include thymosin, lentinan, and PS-K. Examples of peptides of 4000 or lower molecular weight include ACTH, TRH, angiotensin and its analogs, peptide antibiotics, and peptide antitumor substances. Examples of "peptide antibiotics" here include colistin, and examples of "peptide antitumor substances" here include pleomycin and neocarzinostatin. Examples of nucleic acid compounds include citicoline and nucleic acid antitumor substances. Examples of "nucleic acid antitumor substances" here include 5-Fu.

Examples of mercaptoproline derivatives include 3-mercapto-2-methylpropanoyl-proline.

Moreover, when a base has a basic group that forms salts with fatty acids with 8 to 14 carbon atoms or leucine, the base and said acids may be in the form of salts, and this invention also includes such forms.

So long as it can be used as a rectal suppository, the formulation of the suppository of this invention is not subject to special limitations. Examples include standard anal suppositories, and formulations in which a suspension or ointment separated into a liquid oil excipient is enclosed in a soft capsule or tube. Such formulations are prepared by means known in prior art.

Examples of excipients include oil-base and water-base excipients known in prior art. Examples of oil excipients include vegetable oils such as peanut oil, olive oil, corn oil, coconut oil, cacao oil, and fatty acid glycerin esters such as Witepsol® (manufactured by Dynamite Sobel), SB-Base® (manufactured by Kanegafuchi Chemical), O.D.O.® (manufactured by Nissin Oil Mills); and mineral oils such as Vaseline and paraffin. Examples of water-base excipients include polyethylene glycol, propylene glycol, and glycerin.

The composite of this invention is generally manufactured by adding a fatty acid with 8 to 14 carbon atoms or its nontoxic salt to an excipient and dispersing evenly, then adding an above-mentioned base and dispersing evenly. The sequence of addition is not necessarily limited to the sequence given above, and can be selected as desired. Furthermore, additives such as antioxidants, preservatives, masking agents, or other excipients may also be added to these.

The fatty acid with 8 to 14 carbon atoms or its nontoxic salt and

the base preferably have a grain size of 100 mesh or less.

Moreover, fatty acids with 8 to 14 carbon atoms and leucine are generally well-known, and are obtained by hydrolysis of natural oils or standard manufacture of carboxylic acids.

Nontoxic salts of the above-mentioned carboxylic acids are also well-known, and are obtained, for example, by reacting alkali metals or organic bases with said carboxylic acids.

#### Working Example 1

After dissolving 9.47 g Witepsol H-15 (manufactured by Dynamite Sobel) at 40 to 60°C, 0.5 g sodium caprate passed through a 100 mesh sieve was added and stirred well to disperse evenly, then 200 mg potency colistin passed through a 100 mesh sieve were added and dispersed evenly. This was formulated by packing 1 g each into suppository containers, and suppositories were obtained.

Anal suppositories with the compositions shown in the sample column in Table 1 were obtained in the same way.

Suppositories obtained in this way were administered to rabbits, and the amount of each base excreted in urine was measured. The results are shown in Table 1.

Urinary excretion was measured by collecting urine periodically after administering, diluting appropriately, and measuring active concentration by bioassay.

That is, samples were cultured and assayed for 15 to 20 hours at 37°C by the paper disk method following Japanese Antibiotic Basic Guidelines using *Escherichia coli* as the assay organism for peptides and *Bacillus subtilis* for amino acids.

TABLE 1

## URINARY EXCRETION OF BASES

Sample		Urinary Excretion (%)				
Base/Excipient	Carboxylic Acid	0 to 2 hr	2 to 4 hr	4 to 6 hr	Total (0 to 6 hr)	
colistin 20 mg potency Witepsol H-15 1 g total	5% sodium caprate	47.3	10.6	3.2	61.1	
	5% sodium caprylate	40.0	11.1	1.0	52.2	
	5% sodium laurate	37.3	10.0	1.5	48.8	
gentamicin 40 mg potency Witepsol H-15 1 g total	5% sodium caprate	32.0	11.0	9.0	52.0	
gentamicin 40 mg potency Witepsol H-15 1 g total	5% sodium caprate	31.3	13.8	13.8	58.4	
kanamycin 40 mg potency Witepsol H-15 1 g total	5% sodium caprate	30.3	15.8	10.0	55.0	
vacitolacin 40 mg potency Witepsol H-15 1 g total	5% sodium caprate	10.2	8.8	0.5	20.5	

[vacitolacin as transliterated]

[vacitolacin as transliterated]

## Working Example 2

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After dissolving 2.36 g Witepsol H-15 (manufactured by Dynamite Sobel) at 40 to 60°C, 0.125 g sodium caprate passed through a 100 mesh sieve was added and stirred well to disperse evenly, then 15 mg Glu-Trp-Pro-Arg-Pro-Arg-Pro-Glu-Ileu-Pro-Pro (a type of angiotensin I transformed oxygen inhibitor; hereafter called SQ-14225) were added and dispersed evenly. This was formulated by packing 100 mg each into suppository containers, and suppositories were obtained.

10- to 14-week-old Wister spontaneous hypertensive rats (SHR) were prepared in three groups of five rats per group, one of the above-mentioned suppositories (0.6 mg SQ-14225, 5 mg sodium caprate, and 94.4 mg Witepsol H-15) was administered per rectum to the first group, and change over time in mean blood pressure was measured. As controls, this was compared with a group subcutaneously injected 5 ml/kg physiological saline alone, and a group administered 0.6 mg SQ-14225 orally. The results are shown in Table 2.

Mean blood pressure was measured following the method described in *J. Pharmacol. Exp. Ther.*, 204: 281-288 (1978).

## Working Example 3

After dissolving 2.225 g Witepsol H-15 (manufactured by Dynamite Sobel) at 40 to 60°C, 0.125 g sodium caprate passed through a 100 mesh sieve was added and stirred well to disperse evenly, then 0.15 g D-3-mercapto-2-methylpropanol-L-proline (a type of angiotensin I transformed oxygen inhibitor; hereafter called SQ-20881) was added and dispersed evenly. This was formulated by packing 100 mg each into suppository containers, and suppositories were obtained.

10- to 14-week-old SHR were prepared in three groups of five rats

per group, one of the above-mentioned suppositories (6 mg SQ-20881, 5 mg sodium caprate, and 89 mg Witepsol H-15) was administered per rectum to the first group, and change over time in mean blood pressure was measured. As controls, this was compared with a group subcutaneously injected 5 ml/kg physiological saline alone, and a group administered 0.6 mg SQ-20881 orally. The results are shown in Table 3.

Mean blood pressure was measured following the method described in *J. Pharmacol. Exp. Ther.*, 204: 281-288 (1978).

TABLE 2  
MEAN BLOOD PRESSURE (mmHg)

Time	-4	-2	0	2	4	6	8	10	12	14	16
SQ-14225 0.6 mg/head per rectum (n = 5)	180.5	186.9	186.1	155.4	156.0	157.3	160.6	158.4	159.4	164.8	165.5
(Control) SQ-14225 0.6 mg/head per oral (n = 5)	182.5	184.6	181.3	166.0	165.2	160.9	164.1	167.8	167.8	170.0	169.1
(Control) physiological saline 5 mL/kg subcutaneous (n = 5)	184.4	182.9	183.0	184.0	182.6	184.8	186.6	184.1	185.3	183.6	182.7

TABLE 3  
MEAN BLOOD PRESSURE (mmHg)

Time	-4	-2	0	2	4	6	8	10	12	14	16
SQ-20881 6 mg/head per rectum (n = 5)	183.5	184.4	185.5	156.2	157.0	157.8	161.7	160.5	160.8	162.5	163.2
(Control) SQ-20881 6 mg/head per oral (n = 5)	181.4	182.5	180.9	148.8	149.9	156.5	153.3	155.2	156.5	161.0	159.6
(Control) physiological saline 5 mL/kg subcutaneous (n = 5)	186.9	181.8	182.6	184.4	183.3	183.1	181.4	180.5	181.7	184.3	181.5

#### Working Example 4

After dissolving 4.6 g Witepsol H-15 (manufactured by Dynamite Sobel) at 40 to 60°C, 0.2 g sodium caprate was added and stirred well to disperse evenly. Next, 0.2 g 5-Fu powder was added and dispersed evenly. This was formulated by packing 100 mg each into suppository containers, and suppositories were obtained.

The suppositories obtained in this way (4 mg 5-Fu, 5 mg sodium caprate, and 91 mg Witepsol H-15) were administered per rectum to five male rats per group (body weight: approximately 200 g), and blood concentration of 5-Fu was measured. The results are shown in Figure 4.

Blood concentration 5-Fu was measured by collecting from the tail vein periodically after administering, isolating plasma, and measuring active concentration by bioassay. That is, samples were quantified by the cup method using *Staphylococcus aureus* 209P as the assay organism.

TABLE 4  
AFTER ADMINISTERING 5-FU SUPPOSITORIES

Sample		Blood Concentration ( $\mu\text{g/mL}$ )				
Base/Excipient	Fatty Acid	5 min	15 min	30 min	60 min	120 min
5-Fu 4 mg/head Witepsol H-15 1 g total	5% sodium caprate	5.2	11.8	3.1	1.0	0.2
	5% sodium caprylate	4.1	9.9	2.2	1.0	0.1
	5% sodium laurate	5.4	10.0	2.1	0.8	-

#### Working Example 5

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After dissolving 0.949 g Witepsol H-15 at 40 to 60°C, 0.05 g sodium caprate was added and stirred well to disperse evenly. 0.001 g TRH was added to this and stirred well to disperse evenly, then 20 mg weight

bar-shaped anal suppositories were prepared.

The operations described above were repeated except for using sodium caprylate or sodium laurate instead of sodium caprate, and anal suppositories were prepared.

The pharmacological effect of TRH was measured when the suppositories obtained in this way were administered, with the results shown in Figure 5.

Measurement method:  $20 \pm 1$  g male mice were prepared in three groups of six mice per group. Mice in each group were abdominally injected 60 mg/kg phenobarbital sodium salt, then after ten minutes, the first group (control) was subcutaneously injected 1 mL physiological saline containing TRH (TRH: 0.02 mg/head), the second group was administered the above-mentioned anal suppository per rectum, and the third group was subcutaneously injected 0.1 mL physiological saline, and sleep time (minutes) was found. The rate of shortened sleep time due to administering TRH was calculated by the following formula: /7

$$\begin{aligned} &\text{Pharmacological effect (rate of shortened sleep time) =} \\ &[1 - (\text{sleep time due to administering TRH} / \text{sleep time} \\ &\text{due to administering physiological saline})] \times 100 \end{aligned}$$

TABLE 5  
PHARMACOLOGICAL EFFECT OF TIME TRH ADMINISTERED

Sample		Rate of Shortened Sleep Time
Pharmacologically Effective Substance	Fatty Acid	
TRH 0.02 mg/head per rectum	5% sodium caprylate	48.6
	5% sodium caprate	47.6
	5% sodium laurate	48.6 _
(Control) TRH 0.02 mg/head subcutaneous	—	40.8